PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
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International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001256	22.03.2004	20.03.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/205, A23L1/305

Applicant
THE UNIVERSITY OF NOTTINGHAM

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1-7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.01.2005	17.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001256

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-18 as originally filed

Claims, Numbers

1-57 received on 25.04.2005 with letter of 25.04.2005

Drawings, Sheets

1-10 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37-54, 55-57 (partially)

because:

☒ the said international application, or the said claims Nos. 37-54 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 55-57 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-18,20-35,37-54
	No:	Claims	1,2,19,36,55-57
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	1-35, 55-57
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

ITEM I

The amended claims 1-57 fulfill the criteria set by article 34(2)b and are therefore accepted (claim 1 based to old claim 3 and description pages 2-5). There is slight doubt about claim 1 "a composition for increasing carnitine retention in animal/human biological tissue". The description and other original claims mention influencing carnitine retention in the animal/human tissue, but never combine exactly a composition for increasing carnitine retention in animal/human biological tissue, only with animal/human body. Though, there is a method to increase carnitine retention in biological tissue with carnitine and the agent (page 3).

ITEM III

Claims 36-54 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 36-54 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. However such claims as present claims 36-54 do not appear to be novel and inventive for reasons explained later in this written opinion.

Claims 55-57 contain references to the description and examples. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

It is clear from the description on pages 3 and page 4 lines 1-2, page 5 lines 15-18, page 7 lines 19-22, claim 10 that the following features are essential to the definition of the invention:

(1) Carnitine
(2) Agent (carbohydrate, amino acid and protein)
Since independent claims 55-57 do not contain these features they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

ITEM V

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: EP-A-0 680 945 (OMEARA PTY LTD) 8 November 1995 (1995-11-08)

D2: GROSS C J ET AL: "Effect of development and nutritional state on the uptake, metabolism and release of free and acetyl-L-carnitine by the rodent small intestine." BIOCHIMICA ET BIOPHYSICA ACTA. 3 NOV 1993, vol. 1170, no. 3, 3 November 1993 (1993-11-03), pages 265-274, XP008032228 ISSN: 0006-3002

D3: BOHLES H ET AL: "Improved N-retention during L-carnitine-supplemented total parenteral nutrition." JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION. 1984 JAN-FEB, vol. 8, no. 1, January 1984 (1984-01), pages 9-13, XP008032205 ISSN: 0148-6071

D4: GREENWOOD R H ET AL: "Effects of L-carnitine on nitrogen retention and blood metabolites of growing steers and performance of finishing steers." JOURNAL OF ANIMAL SCIENCE. JAN 2001, vol. 79, no. 1, January 2001 (2001-01), pages 254-260, XP002286196 ISSN: 0021-8812

D5: LACOUNT D W ET AL: "Responses of dairy cows during early lactation to ruminal or abomasal administration of L-carnitine." August 1995 (1995-08), JOURNAL OF DAIRY SCIENCE. AUG 1995, VOL. 78, NR. 8, PAGE(S) 1824 - 1836 , XP002286406 ISSN: 0022-0302

D6: LACOUNT D W ET AL: "Dose response of dairy cows to abomasal administration of four amounts of L-carnitine." April 1996 (1996-04), JOURNAL OF DAIRY SCIENCE. APR 1996, VOL. 79, NR. 4, PAGE(S) 591 - 602 , XP002286407 ISSN: 0022-0302

D7: LACOUNT D W ET AL: "Ruminal degradation and dose response of dairy cows

to dietary L-carnitine." February 1996 (1996-02), JOURNAL OF DAIRY SCIENCE. FEB 1996, VOL. 79, NR. 2, PAGE(S) 260 - 269 , XP002286408 ISSN: 0022-0302

D8: WO 01/95915 A (SIGMA TAU HEALTHSCIENCE SPA ; POLA PIETRO (IT)) 20 December 2001 (2001-12-20)

2. NOVELTY OBJECTIONS

A composition claim containing for example "for increasing carnitine retention" and "agent to increase blood/plasma insulin concentration" means only a composition/ agent, which is suitable for stated use (PCT international search and preliminary examination guidelines Chapter 5.23). In a composition/product claim the use is not regarded as such a limitation.

D1 describes the use of carnitine in feed and food supplements with amino acids to improve carnitine retention in human/animal tissues. (page 2, line 39- page 3, line 47, page 4 lines 36-51). Consequently, the subject matter of claims 1,2,19,36,55-57 is considered as being not new in view of D1 (Art 33 (2) PCT).

D2 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (sucrose) to improve carnitine retention in human/animal tissues. Samples studied from intestine and mucosa. (page 265, paragraph 1- page 266, paragraphs 1,6,7, page 268, paragraph 1- page 270, paragraph 3, page 272, paragraph 3- page 273, paragraphs 2,4,5). Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D2 (Art 33 (2) PCT).

D3 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (sucrose) to improve carnitine retention. Samples studied from serum and urine. (page 9, paragraph 1,2,5, page 11, paragraphs 3,6,8- page 12, paragraph 2). Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D3 (Art 33 (2) PCT).

D4 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates (molasses) to study carnitine retention. Samples studied from kidney, pelvic, heart, blood, plasma (page 254 paragraph 1,4, page 256, paragraph 5, page 257,

paragraph 2,4,6, page 259, paragraph 5 page 260 paragraph 1,3, tables 1,2). Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D4 (Art 33 (2) PCT).

D5 describes the use of carnitine in feed supplements (protein, amino acids, molasses and carbohydrates) to study carnitine retention. Samples studied from, blood, tissue, muscle, liver (page 1824 paragraph 1, page 1825, paragraph 3, page 1827, paragraph 3-5, page 1828, paragraph 3- page 1829 paragraph 2, page 1835 paragraph 2, table 1).Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D5 (Art 33 (2) PCT).

D6 describes the use of carnitine in feed supplements (protein, amino acids and carbohydrates) to study carnitine retention. Samples studied from plasma, blood,urine. (page 591, paragraph 3, page 593, paragraph 3, page 594, paragraph 3, page 596, paragraph 3, page 597, paragraphs 3,4, page 601, paragraph 2, tables 1,2,4,7) . Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D6 (Art 33 (2) PCT).

D7 describes the use of carnitine in feed supplements (protein, amino acids, molasses and carbohydrates) to study carnitine retention. Samples studied from plasma, blood,urine. (page 260, paragraphs 1,2,4- page 261, paragraph 2, page 262, paragraph 2, page 263, paragraph 45, page 267, paragraphs 3). Consequently, the subject matter of claims 1,2,36,55-57 is considered as being not new in view of D7 (Art 33 (2) PCT).

D8 describes the use of carnitine in food supplements (protein, amino acids, carbohydrates) to improve muscle performance (page 1, paragraph 1- page 2, paragraph 1, page 6, paragraph 3- page 9, paragraph 1). Consequently, the subject matter of claims 1,55-57 is considered as being not new in view of D8 (Art 33 (2) PCT).

3. INVENTIVE STEP OBJECTIONS

Dependent claims 3-18,20-35,37-54 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:

The features of dependent claims 3-18,20-35,37-54 have already been employed for the same purpose (D1 (claims 3-18,20-35,37-54), D2-D7 (claims 3-18, 37-54), D8 (claims 3-18)). It would therefore be obvious to the person skilled in the art, to apply these features with corresponding effect. Consequently, the subject matter of claims 3-18,20-35,37-54 is considered as being not inventive in view of D1-D8 (Art 33(3) PCT).

None of the claimed compositions, uses or methods are considered to be inventive in view of D1-D8 (Art 33(3) PCT). Having regard to the claimed compositions, uses or methods and the prior art known (D1-D8), it is considered that the man skilled in the art would regard these compositions, uses or methods of the present invention (as far as novel) as an obvious alternative to those known.

CLAIMS

1. A composition for increasing carnitine retention in the animal and/or human biological tissue, the composition comprising a carnitine substance and an agent to increase blood/plasma insulin concentration.

2. A composition for use in the manufacture of a medicament to influence carnitine retention in the animal and/or human biological tissue, the composition comprising a carnitine substance and an agent to stimulate insulin release in the body.

3. A composition according to claim 1 or 2 wherein the agent is operable to increase sodium dependent carnitine uptake into tissue cells, in particular skeletal muscle, liver and/or kidney cells.

4. A composition according to any preceding claim wherein the agent is operable to increase insulin activity in the tissue.

5. A composition according to claim 4 wherein the agent is operable to increase insulin activity in the tissue by increasing the amount of insulin in the blood/plasma.

6. A composition according to any preceding claim wherein the agent comprises a carbohydrate, and/or an active derivative thereof, and/or an amino acid and/or a protein.

7. A composition according to claim 6 wherein the agent is a carbohydrate and/or a derivative of a carbohydrate.

8. A composition according to claim 6 or 7 wherein the carbohydrate is a simple carbohydrate, and/or the derivative of the carbohydrate is a derivative of a simple carbohydrate.

9. A composition according to claim 7 wherein the carbohydrate is a simple sugar, and/or the derivative of the carbohydrate is a derivative of a simple sugar.

10. A composition according to claim 8 or 9 wherein the carbohydrate comprises glucose, sucrose, and/or fructose, and/or the derivative of the carbohydrate is a derivative of glucose, sucrose and/or fructose.

11. A composition according to any preceding claim wherein the amount by weight of the agent is between 10 and 150 times the amount by weight of the carnitine substance.

12. A composition according to any preceding claim wherein the amount by weight of the agent is between 10 and 95 times the amount by weight of the carnitine substance.

13. A composition according to any preceding claim wherein the amount by weight of the agent is between 10 and 40 times the amount by weight of the carnitine substance.

14. A composition according to any preceding claim comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 450g of the agent.

15. A composition according to any preceding claim comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 285g of the agent.

16. A composition according to any preceding claim comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 120g of the agent.

17. A composition according to any preceding claim in the form of a solution.

18. A composition according to any preceding claim in the form of an aqueous solution.

19. A food supplement comprising a carnitine substance and an agent to increase blood/plasma insulin concentration.

20. A food supplement according to claim 19 wherein the agent is operable to increase sodium dependent carnitine uptake into tissue cells, in particular skeletal muscle, liver and/or kidney cells.

21. A food supplement according to claim 19 or 20 wherein the agent is operable to increase insulin activity in the tissue.

22. A food supplement according to claim 21 wherein the agent is operable to increase the insulin activity in the tissue by increasing the amount of insulin in the blood/plasma.

23. A food supplement according to any of claims 19 to 22 wherein the agent comprises a carbohydrate, and/or an active derivative thereof and/or an amino acid and/or a protein.

24. A food supplement according to claim 23 wherein the agent is a carbohydrate and/or a derivative of a carbohydrate.

25. A food supplement according to claim 23 or 24 wherein the carbohydrate is a simple carbohydrate and/or the derivative of the carbohydrate is a derivative of a simple carbohydrate.

26. A food supplement according to claim 25 wherein the carbohydrate is a simple sugar, and/or the derivative of the carbohydrate is a derivative of a simple sugar.

27. A food supplement according to claim 24 or 25 wherein the carbohydrate comprises glucose, sucrose and/or fructose, and/or the derivative of the carbohydrate comprises a derivative of glucose, sucrose and/or fructose.

28. A food supplement according to any of claims 19 to 27 wherein the amount by weight of the agent is between 10 and 150 times the amount by weight of the carnitine substance.

29. A food supplement according to any of claims 19 to 28 wherein the amount by weight of the agent is between 10 and 95 times the amount by weight of the carnitine substance.

30. A food supplement according to claims 19 to 29 wherein the amount by weight of the agent is between 10 and 40 times the amount by weight of the carnitine substance.

31. A food supplement according to claims 19 to 30 comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 450g of the agent.

32. A food supplement according to any of claims 19 to 31 comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 285g of the agent.

33. A food supplement according to any of claims 19 to 32 comprising substantially 0.25g to 3g carnitine substance and between 2.5g and 120g of the agent.

34. A food supplement according to claims 19 to 33 in the form of a solution.

35. A food supplement according to any of claims 19 to 34 in the form of an aqueous solution.

36. A method of increasing carnitine retention in the animal and/or human biological tissue, the method comprising administering to the body a carnitine substance and an agent to increase blood/plasma insulin concentration.

37. A method according to claim 36 wherein the method increase carnitine retention in the tissue by increasing the transportation of the carnitine substance, or a derivative thereof into tissue cells.

38. A method according to claim 37 wherein transportation is increased by stimulation of a sodium dependent transport protein and substantially simultaneously increasing blood/plasma carnitine concentration.

39. A method according to any of claims 36 to 38 wherein the agent is operable to increase sodium dependent carnitine uptake into tissue cells, in particular skeletal muscle, liver and/or kidney cells.

40. A method according to any of claims 36 to 40 wherein the agent is operable to increase insulin activity in the tissue.

41. A method according to claim 40 wherein the agent is operable to increase insulin activity in the tissue by increasing the amount of insulin in the blood/plasma.

42. A method according to any of claims 36 to 40 wherein the agent comprises a carbohydrate, and/or an active derivative thereof, and/or an amino acid and/or a protein.

43. A method according to claim 42 wherein the agent is a carbohydrate and/or a derivative of a carbohydrate.

44. A method according to claim 42 or 43 wherein the carbohydrate is a simple carbohydrate, and/or the derivative of the carbohydrate is a derivative of a simple carbohydrate.

45. A method according to claim 44 wherein the carbohydrate is a simple sugar, and/or the derivative of the carbohydrate is a derivative of a simple sugar.

46. A method according to claim 44 or 45 wherein the carbohydrate comprises glucose, sucrose and/or fructose, and/or the derivative of the carbohydrate is a derivative of glucose, sucrose and/or fructose.

47. A method according to any of claims 36 to 46 wherein the method involves oral administration and ingestion of the carnitine substance and agent.

48. A method according to claim 47 wherein the oral administration and ingestion of the carnitine substance and the agent occurs simultaneously.

49. A method according to any of claims 36 to 48 wherein the amount by weight of the agent is between 10 and 150 times the amount by weight of the carnitine substance.

50. A method according to any of claims 36 to 49 wherein the amount by weight of the agent is between 10 and 95 times the amount by weight of the carnitine substance.

51. A method according to any of claims 37 to 51 wherein the amount by weight of the agent is between 10 and 40 times the amount by weight of the carnitine substance.

52. A method according to any of claims 36 to 51 wherein substantially 0.25g to 3g of the carnitine substance and between 2.5g and 450g of the agent are administered.

53. A method according to any of claim 30 to 52 when substantially 0.25g to 3g of the carnitine substance and between 2.5g and 285g of the agent are administered.

54. A method according to any of claims 36 to 53 wherein substantially 0.25g to 3g of the carnitine substance and between 2.5g and 120g of the agent are administered.

55. A composition substantially as herein described with reference to Example I, II or III.

56. A food supplement substantially as herein described with reference to Examples I, II or III.

57. A method substantially as here described with reference to Examples I, II or III.